Haploinsufficiency of MEOX2 impairs nociception signaling by reducing action potential frequency

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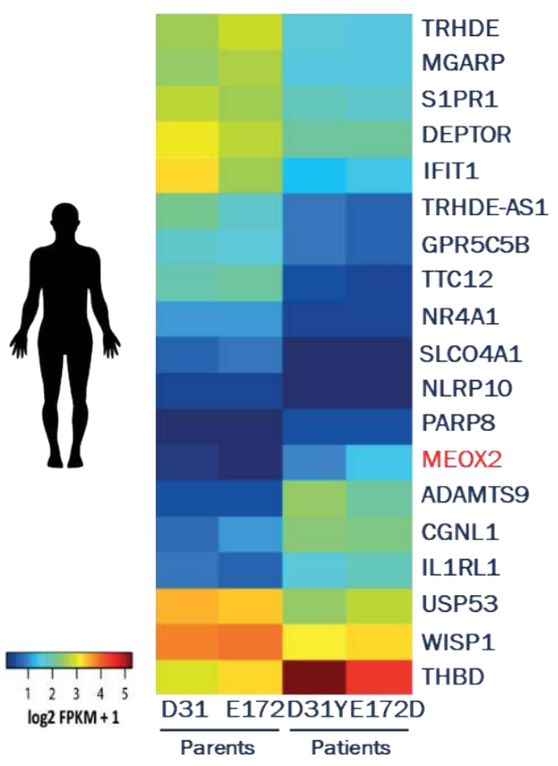
Congenital Insensitivity to Pain (CIP) is a rare genetic disorder of the nociceptors, neurons specialized in responding to noxious stimuli. Several genetic causes of the disorder have been identified, including mutations in a gene encoding for PRDM12 protein. In human patient fibroblasts of PRDM12-CIP patients we find *MEOX2* to be dysregulated. Here we aim to characterize the novel role for MEOX2 in pain perception.

MEOX2 is dysregulated in CIP patient fibroblasts

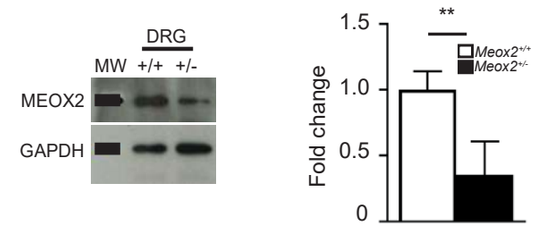
Fibroblast transcriptome analysis revealed *MEOX2* to be significantly deregulated in fibroblast of patients suffering from PRDM12-associated CIP. *MEOX2* encodes for homeobox protein MOX-2, a transcriptional factor involved in mesoderm patterning, somite differentiation, myocyte development. It's function in sensory neurons is completely unknown.



Heat map of the 19 genes significantly deregulated in fibroblasts from patients carrying mutations in *PRDM12* as compared to their respective first order relatives.

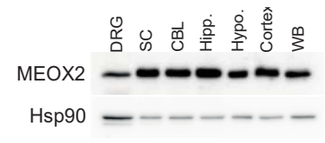
Mouse model

- Classical *Meox2*$^{-/-}$ KO neonatally lethal
- Heterozygous *Meox2*$^{+/-}$ viable

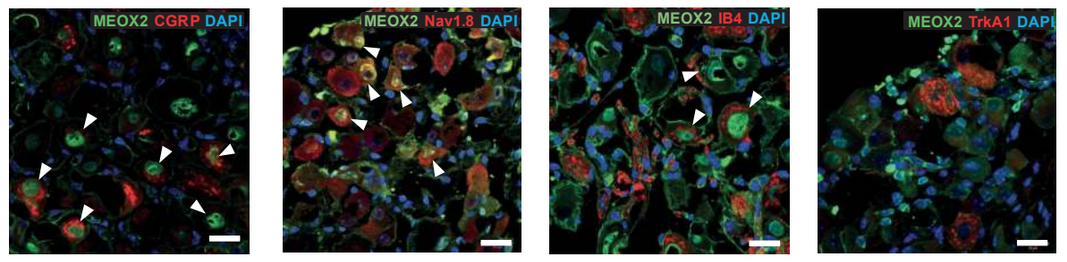


MEOX2 protein and mRNA levels decreased in Meox2+/- DRGs.

MEOX2 is expressed in nociceptors

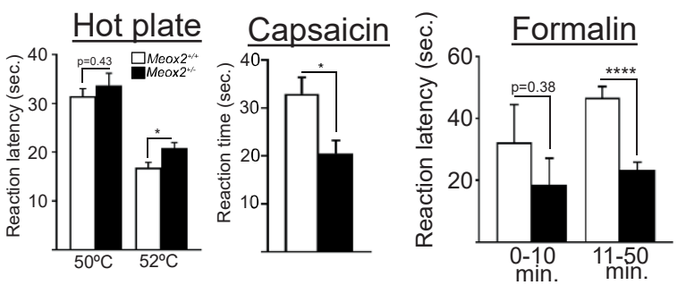


MEOX2 is expressed throught the nervous system, including dorsal root ganglia.



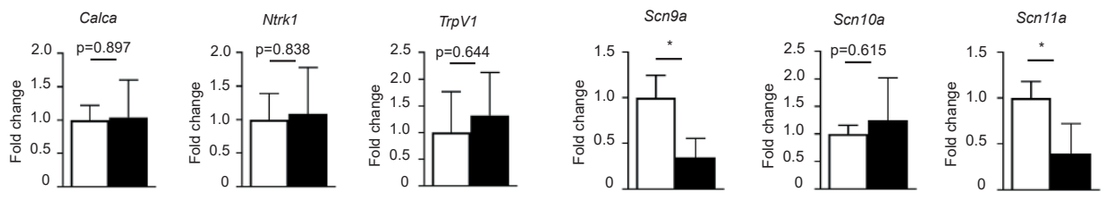
Sections of adult wild-type DRGs were co-immunolabled with antibodies against MEOX-2 and selected markers of nociceptors, showing colocalization of MEOX2 with CGRP, Nav1.8, IB4, but not TrkA.

Meox2$^{+/-}$ animals show impaired pain perception



Meox2$^{+/-}$ animals show decreased sensitivity to acute pain on hot plate at 52 °C (left), capsaicin injection (middle) as well as inflammatory pain – second phase of formalin test (right)..

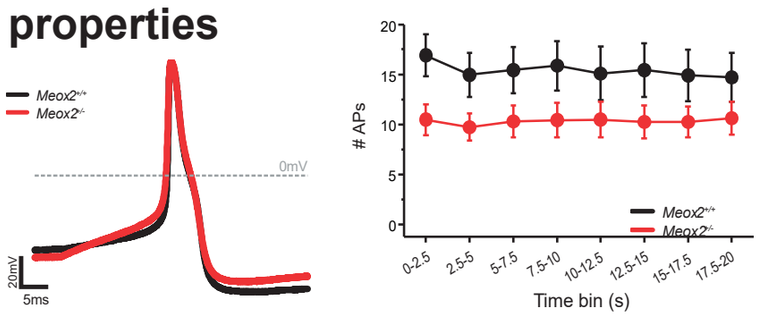
Meox2$^{+/-}$DRGs show decreased *Scn9a* and *Scn11a* mRNA levels in RT-qPCR



mRNA for nociceptor markers *Claca*, *Ntrk1* and *Trpv1* are not dysregulated in *Meox2*$^{+/-}$ DRGs.

mRNA of voltage gated sodium channels *Scn9a* and *SCn11a*, but not *Scn10a* are significantly decreased in *Meox2*$^{+/-}$ DRGs.

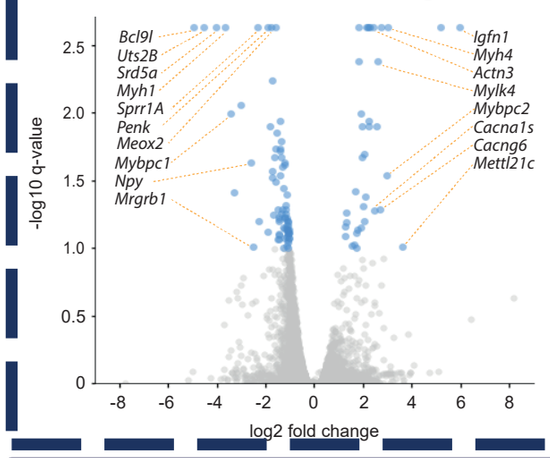
Meox2$^{+/-}$DRG neurons show impaired electrophysiological properties



Representative traces of action potential generation upon a depolarizing pulse.

Meox2+/- cultured DRGs generated significantly less action potential numbers in a prolonged stimulation (left) and ramp-shaped depolarization that is 1-, 2- and 3-times the individual Rheobase.

Transcriptome analysis of *Meox2*$^{+/-}$DRGs



Transcriptome analysis of Meox2+/- DRGs reveals downregulation of several pain genes, including neuropeptides *Npy*, *Penk* and *Uts2b*, while upregulated are genes involved in muscle function and development (*Myh4, Actn3, Mylk5*).

Conclusion

- **MEOX2 is expressed in dorsal root ganglia neurons.**
- ***MEOX2*$^{+/-}$ heterozygous dorsal root ganglia neurons trigger less action potentials.**
- ***MEOX2*$^{+/-}$ show downregulated *Scn9a* and *Scn11a*, providing a framework for decreased AP firing.**

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Nagy V., et al., 2015, The evolutionary conserved transcription factor PRDM12 controls sensory neuron development and pain perception, Cell Cycle, 14:12, 1799-1808.

*Contributed equally , #co-corresponding